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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,938	SONG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,13-15 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8-12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/14/06; 10/03/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner and Art Unit handling this application have changed. Please address further correspondence to Richard Schnizer, Art Unit 1635, whose contact information is given at the end of this Action.

An amendment was received and entered on 5/13/09. Applicant's election group 2 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 4, 5, 7, 13-15, and 20-25 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/13/09. Claims 18 and 19 were withdrawn from consideration by Applicants amendment filed 5/13/09.

Claims 1-3, 6, 8-12, and 16 are under consideration in this Office Action.

Specification

Applicant is advised that, in the electronic file for the application, the specification has two identical page 19s. In the event application is otherwise allowable, the Examiner will need Applicant's permission to delete one of the two page 19s.

Drawings

No drawings were filed with the application.

Oath/Declaration

The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602. While the title of he invention is listed at the top of the Declaration filed 2/23/07, The declaration does not specify whether it is directed to "the attached application" or a specific attorney docket number filed on a particular date.

Claim Interpretation

The claims require an assay system capable of detecting RANBP2 expression or activity comprising a purified RANBP2 nucleic acid. The specification as filed does not define the term "purified" in the context of nucleic acids. The specification addresses this term in the context of proteins at e.g. paragraph 26, indicating that proteins can be purified by ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis; or immunoaffinity purification. These are all procedures that remove the protein from a cell. The specification also implies at paragraph 70, that the term "purified" correlates with "cell-free", i.e. "[t]he term "cell free" encompasses assays using substantially purified protein". Thus one of skill might come to the conclusion that by "purified RANBP2 nucleic acid" the claims meant a nucleic acid that was removed from a cell, such that the recited assay had to be cell-free. However, this interpretation would render indefinite claims 2, 3, and 6 since these claims would be

interpreted in view of the specification as a whole to require cells comprising the "purified" RANBP2 nucleic acid.

The relevant prior art provides different definitions of "purified" as it applies to nucleic acids. For example US 6545140, states that "[a]s used herein, the terms "isolated and/or purified" refer to in vitro preparation, isolation and/or purification of a nucleic acid molecule, polypeptide or peptide of the invention, so that it is not associated with in vivo substances and is substantially free of infectious agents.

US 6545143 claims methods of purifying nucleic acids by non-covalently binding nucleic acids from a sample to particles having a glass surface, removing non-bound sample components and eluting the bound nucleic acids from the glass surface, wherein the sample is contacted with a preparation of particles having a glass surface, comprising more than 75% by weight of these particles having a particle size between 0.5 and 15 microns, wherein more than 95% by weight of the particles having a particle size between 0.5 and 15 microns are magnetic.

Both US 6545140 and 6545143 would seem to exclude nucleic acids within cells from the genus of "purified" nucleic acids.

On the other hand, US 6551795 indicates that a "purified or isolated or a substantially purified nucleic acid e.g., a substantially pure DNA, (are terms used interchangeably herein) is a nucleic acid which is one or both of the following: not immediately contiguous with both of the coding sequences with which it is immediately contiguous (i.e., one at the 5' end and one at the 3' end) in the naturally-occurring genome of the organism from which the nucleic acid is derived; or which is substantially

free of a nucleic acid with which it occurs in the organism from which the nucleic acid is derived. The term includes, for example, a recombinant DNA which is incorporated into a vector, e.g., into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (e.g., a cDNA or a genomic DNA fragment produced by PCR or restriction endonuclease treatment) independent of other DNA sequences."

This last definition is found to be the broadest reasonable definition that is consistent with the specification as filed and the claims as amended, because this definition would allow for assays that are cell based and that comprise recombinant expression vectors encoding RANBP2. Accordingly the phrase "purified RNABP2 nucleic acid" is interpreted as meaning a nucleic acid which is one or both of the following: not immediately contiguous with both of the coding sequences with which it is immediately contiguous (i.e., one at the 5' end and one at the 3' end) in the naturally-occurring genome of the organism from which the nucleic acid is derived; or which is substantially free of a nucleic acid with which it occurs in the organism from which the nucleic acid is derived.

Having said all this, the Examiner notes that Applicant may wish to consider deleting "purified RANBP2 nucleic acid" from the claim, and replacing it with "recombinant expression construct capable of expressing a RANBP2 polypeptide", which is supported in the specification at page 9, lines 24-32, and page 10, line 28 to page 13, line 20. If Applicant prefers "expression vector" to "expression construct", there is *ipsis verbis* support for "expression vector" at page 9, line 25.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, 8-12, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6, 8-12, and 16 are indefinite because it is unclear what are the metes and bounds of the claim term "RANBP2". The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Further, it is unclear if Applicant intends RANBP2 to embrace terms such as RANBP2L1, which is the designation for a divergent duplication of a RANBP2 locus (see Northwang et al (Genomics 47: 383-392, 1998)). Amending the claims to specifically and uniquely identify RANBP2 polypeptides and polynucleotides by SEQ ID NOS can obviate the rejection.

Claim 10 is indefinite in its recitation of "phosphothioate morpholino oligomers (PMO)". It is unclear if applicant's are being their own lexicographers and are redefining the art recognized term "PMO" to mean "phosphothioate morpholino", or whether Applicant intends to claim an oligomer that has both phosphorothioate and phosphorodiamidate linkages. The specification at page 19, lines 18-22 is ambiguous

in this regard. Note that the term "PMO" is recognized by those of ordinary skill to mean "phosphorodiamidate morpholino".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-3, 6, 8-12, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the genus of purified RANBP2 nucleic acids that encode polypeptides that have RANBP2 activity. The specification as filed indicates that the nucleic acids can encode full length RANBP2 or active fragments. While the specification indicates that it is preferable that RANBP2 nucleic acids should be at least 70% identical to human RANBP2 nucleic acids, no lower limit of required identity is set forth.

The prior art indicates that RANBP2 has a variety of functions. It is a giant scaffold and mosaic cyclophilin-related nucleoporin implicated in controlling selective processes of the Ran-GTPase cycle. RANBP2 is a vertebrate mosaic protein composed of four interspersed RanGTPase binding domains (RBDs), a variable and species

specific zinc finger cluster domain, leucine-rich, cyclophilin, and cyclophilin-like (CLD) domains. Subregions within or between these domains associate specifically with the nuclear export receptor CRM1/exportin-1, components of the 19 S regulatory particle of the 26 S proteasome, and kinesin microtubule-based motor proteins, KIF5B and KIF5C (Cai et al (J. Biol. Chem. 276(45):41594-41602, 2001)). Note that the KIF5B and KIF5C binding domain appears to be present in related RanBP2L1, but leads to the neuronal association of only RanBP2 with two kinesin microtubule-based motor proteins, KIF5B and KIF5C (see abstract and page 41599 of Cai (2001)). Thus the context in which this domain occurs appears to be critical to its function inasmuch as its placement in the highly homologous RANBP2L1 does not lead to KIF5B and KIF5C binding activity. RANBP2 also has enzymatic activity, i.e. SUMO1 E3 ligase activity (see Pichler et al (Cell 106: 109-120, 2002).

The specification as filed discloses the presence in RANBP2 of RanBP1 binding domains and zinc finger domains at page 36. However, while the specification provides general guidance as to which amino acids are considered to have similar properties (page 7) it provides no description whatsoever of which amino acid residues are required for any of the diverse binding or catalytic activities of RANBP2, or which amino acids can be substituted without loss of any or all of these binding and catalytic activities. Those of skill in the art appreciate that the function of a given amino acid within a protein is a function of its microenvironment, i.e. the three dimensional space around the amino acid. Thus, for example, a substitution of an aspartate residue for a glutamate residue may not preserve function, despite the fact that both are negatively

charged at physiological pH. This can be due to the fact that aspartate has one less carbon in its side chain, such that the aspartate acidic moiety may not be able to interact with neighboring moieties in the same way as the glutamate moiety. See e.g. Lazar *et al.* (Mol. Cell Biol. 8:1247-1252, 1988) who taught that replacement of aspartate at position 47 with glutamate sharply reduced the biological activity of transforming growth factor alpha. Accordingly determinations as to which amino acid substitutions are allowable in a given protein is generally made empirically and must be provided on a case by case basis.

The specification as filed discloses 6 RANBP2 nucleic acid sequences (SEQ ID NOS: 1-6). SEQ ID NOS: 1 is 10697 nucleotides in length and encodes a full length RANBP2 (3224 amino acids). SEQ ID NO: 2 10005 nucleotides long, but is identical to SEQ ID NO: 1 over its entire length. SEQ ID NO: 3 is 2208 nucleotides long and has 7 nucleotide differences from SEQ ID NO: 1, including frameshifts at nucleotides 1507 and 2194. SEQ ID NO: 4 is 4208 nucleotides long and has only 2 mismatches to SEQ ID NO: 1. SEQ ID NO: 5 is 2146 nucleotides long is has 4 mismatches to SEQ ID NO: 1. SEQ ID NO: 6 is 1026 nucleotides long is has 8 mismatches to SEQ ID NO: 1. Each of SEQ ID NOS:3-6 corresponds to the 3' end of SEQ ID NO: 1. It is not disclosed whether or not any of these mismatches results in an amino acid change. The specification does not disclose what activity any of SEQ ID NOS: 3-6 encodes.

The written description requirement for genus claims can be satisfied by disclosure of a representative number of species of the genus, either by reduction to practice, complete structural description, or disclosure of critical structure/function

relationships that are common to the members of the genus. The instant specification does not disclose a representative number of species of the genus RANBP2 nucleic acids that encode RANBP2 polypeptides with RANBP2 activity because it fails to teach a what portions of RANBP2 are required for which activities, and which nucleic acid sequences that vary from SEQ ID NO: 1 will encode a functional RANBP2.

Enablement

Claims 1-3, 6, 8-12, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of identifying a candidate PTEN/IGF pathway modulating agent comprising providing an assay system capable of detecting RANBP2 expression or activity, contacting the assay system with a test agent, and determining expression or activity of RNABP2 in the assay system, wherein a change in RANBP2 expression or activity between the presence or absence of the agent identifies the agent as a candidate PTEN/IGF pathway modulating agent. Accordingly the enablement of the invention depends upon the establishment of a link between RANBP2 and the PTEN/IGF pathway.

The specification discloses the results of a synthetic lethal screen in which cultured cells Drosophila cells (Schneider S2) were treated for three days with siRNA

directed to PTEN, subsequently stimulated for an undisclosed time with insulin, and then plated and exposed to siRNA against CG11856. CG11856 is a designation for a Drosophila gene encoding nucleoporin 358 (nup358). The specification indicates that RANBP2 is a human ortholog of nup358 and shares 27% amino acid identity with it . A cell proliferation assay was then used to quantify cell viability, compared to PTEN down-regulated and insulin-stimulated control cells receiving siRNA against luciferase. The results were that "CG11856 reduced the viability of insulin and dPTEN dsRNA treated cells." From this, the Examiner infers that treatment with siRNA directed against CG11856 led to a reduction in lethality, since these cells would have reduced CG11856 gene product, and CG11856 reduced the viability of insulin and dPTEN dsRNA treated cells. From this experiment, and from the finding that RANBP2 is a human ortholog of the CG11856 gene product, Applicant infers that there is a link between RANBP2 and the PTEN/IGF pathway. There is no guidance as to which particular structural or functional characteristic of RANBP2 is required for this link, or as to which binding or catalytic activity, or combination of activities is responsible.

The prior art indicates that RANBP2 and nup358 are each associated with the cytoplasmic face of the nuclear pore in their respective organisms, and that they function in trafficking of macromolecules through the pore, thus they share some functional characteristics. However, a comparison of the two proteins shows that their structural similarity is scant. The specification at page 35 indicates that RANBP2 and nup358 share only 27% amino acid sequence identity. Nup358 has a only a single zinc finger domain, whereas human RANBP2 has 8 zinc finger domains, as well as a

cyclophilin-like domain and an E3 ligase, neither of which appear to be present in nup358. Note that even though related protein RANBP2L1 appears to comprise the RANBP2 KIF5B and KIF5C binding domain, and is otherwise highly homologous to RANBP2, this domain does not appear to be active in the context of RANBP2L1 (see abstract, and paragraph bridging columns on page 41599 of Cai (2001)). This is direct evidence of the effect that sequence differences can have in protein function. Accordingly one of skill in the art appreciates that proteins of only 27% identity are likely to have functional differences, and would not necessarily assume that just because one of the proteins had a relationship with a given pathway, such as the PTEN/IGF pathway, the other protein did as well. It should be noted as well that, even if the specification were enabling for assays using nucleic acids encoding SEQ ID NO: 7, the claims read on a vast genus of variants, homologs, and orthologs, and their variants as well. As discussed above under written description, the specification as filed fails to provide adequate description or guidance as to which variants, homologs, and orthologs would retain the required activity, nor even what that activity may be.

In view of the unpredictable nature of protein structure/function relationships as discussed above, the lack of evidence linking RANBP2 to the PTEN/IGF pathway, the breadth or RANBP2 proteins encompassed by the claims, the lack of guidance regarding which structural features of RANPB2 would be necessary and sufficient to affect the PTEN/IGF pathway, and the lack of guidance as to how those structural features could be modified while retaining the requisite activity, one of skill in the art would have to perform undue experimentation in order to practice the invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yokoyama et al (Nature 376: 184-188, 1995), Bennett et al (Curr. Opin. Mol. Ther. 1(3) : 359-371), Gewirtz (US 5,612,212)

Yokoyama taught a cDNA encoding (RANBP2) and began to characterize the encoded protein, including attempting to determine its function by inhibiting its activity in cultured cells that expressed the protein, through the use of RANBP2 antibodies. See entire document, e.g. Figs. 1B and 3C.

It was routine in the art at the time of the invention to investigate protein function by inhibiting expression of the protein in question through the use of antisense oligonucleotides. See e.g. Bennett et al (Curr. Opin. Mol. Ther. 1(3) : 359-371). Furthermore, it was well understood that the stability of antisense oligonucleotides could be improved by incorporating modifications such as phosphorothioate and morpholino linkages (see Gewirtz at column 6, lines 8-34). Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to inhibit the expression of RANBP2 by administration of antisense oligonucleotides, inasmuch as there was a desire to understand the function of RANBP2. Such studies would have been confirmatory of the results obtained with the antibody experiments. And it would have

been similarly obvious to stabilize the oligonucleotides with art recognized modifications such as phosphorothioate and morpholino linkages.

The references summarized above do not address antisense inhibition of expression of a "purified RNABP2 nucleic acid", i.e. one that is not in its natural genomic context. However, expression of recombinant proteins from expression constructs, either chromosomal (transgene) or plasmid-based, were extremely well known in the art at the time of the invention. It would have been obvious to use such constructs in several research scenarios. For example, it is routine in the art to examine protein structure and function by providing a mutated version of a given protein to a cell via a recombinant expression construct. According to Yokoyama in the legend to Fig. 1 at page 184, RANBP2 comprised many regions of homology to other proteins. The function of any of these could be investigated by making appropriate mutations in the corresponding region of the cDNA, and expressing the mutants in a cell. A relationship between the mutant and any phenotypic change, such as a perturbation of nuclear pore structure or function, could be confirmed by using antisense specific to the mutant, which would be expected to relieve such a phenotypic change. Alternatively, one could determine if homologous forms of RANBP2 could complement each other, e.g. by knocking out the mouse locus in mouse cells, and complementing the deficiency with an expression vector for the human RANBP2. Complementation could be confirmed through the use of antisense directed against RANBP2, which would be expected to have a deleterious effect.

In summary all of the recited materials and method steps were known in the prior art, and there were sound scientific reasons for combining them in the way required by the instant claims. Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635